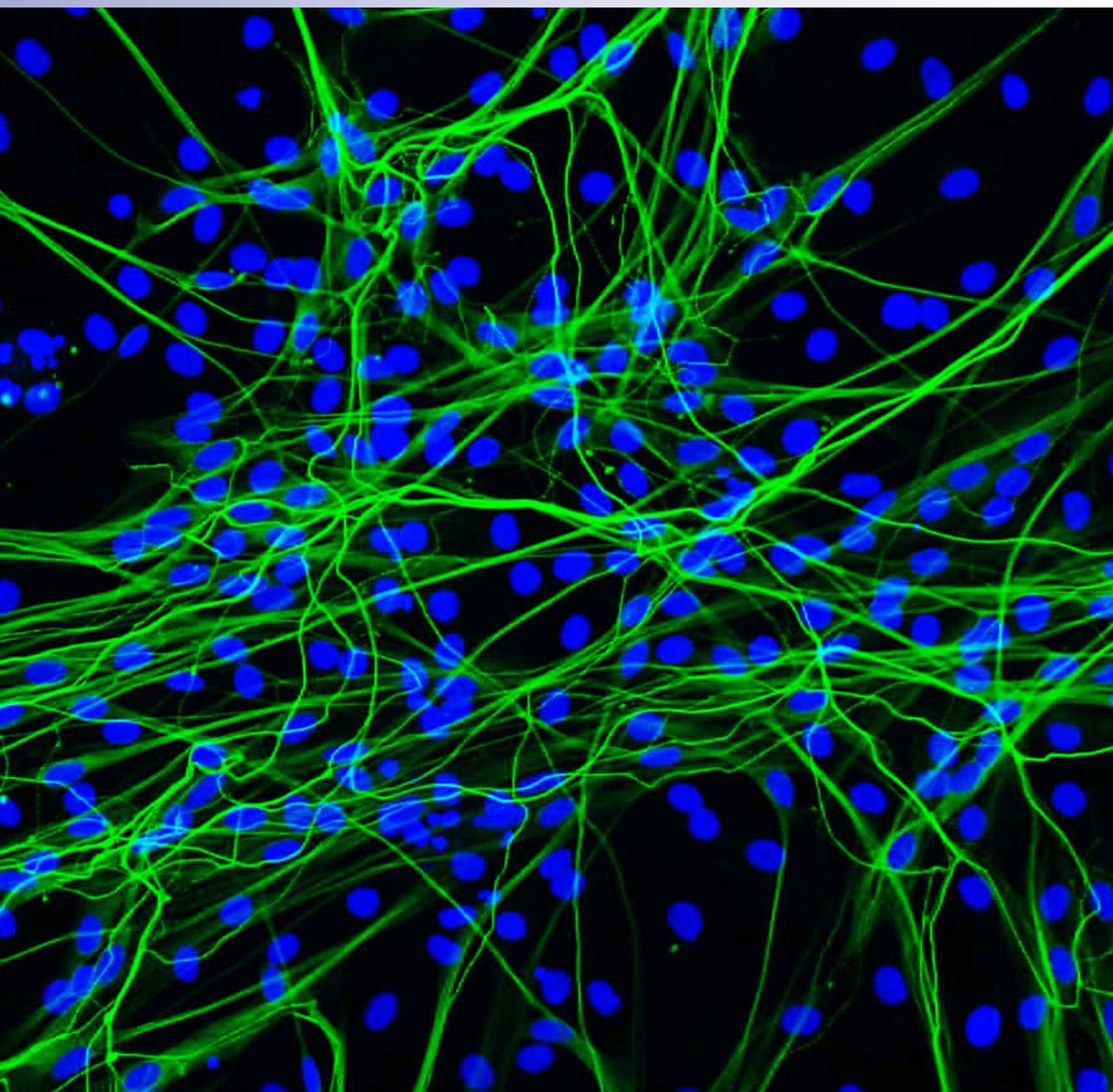


JOINT MEETING ON NEW CELL THERAPIES

Wednesday, 23rd November 2016, 9.00 am to 5.30 pm
Langhans Auditorium, Inselspital, University of Bern



ACCREDITATION

Swiss Society of Surgery (SGC-SSC): 6 Credits

Swiss Society of Ophthalmology (SOG-SSO): 6 Credits

Swiss Neurological Society (SNG-SNS): 1 Credit

Swiss Society of Dermatology and Venereology (SGDV-SSDV): 6 Credits

Swiss Society of Hematology (SGH-SSH): 6 Credits

MEETING ASSISTANT

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DEAR CELL THERAPY AND STEM CELL SPECIALISTS

On behalf of SCRM and SICT, it is our great pleasure to invite you to the first joint meeting of both societies in Bern in November 2016.

This first joint meeting is intended as a starting signal for new cooperations in the field of cell therapies. Its main aim is to promote collaborations and to generate synergies among cell therapy centers in Switzerland.

As organizers of the meeting, we are pleased to announce that we will bring representatives of all five University Centers for cell therapy to one table. Following short presentations from these University Centers, we will have a round table discussion on how to «Establish a cooperative network between Swiss Cell Therapy Centers for Innovation and Success». Moreover, specialists from the Swiss University Centers and external speakers will share their expertise in the field of regenerative medicine, with a special focus on bridging cell-based therapies on a national and international level.

We cordially invite you to join our meeting in Bern, attend the lectures, meet colleagues, discuss timely topics, and learn about the exciting developments in the field of cell therapies.

Prof Dr Thomas Krause

President Organizing Committee
Member SCRM Platform

Ms Thérèse Meyer-Kaelin

President SICT

Organizing Committee

Prof Dr Thomas Krause
Prof Dr Volker Enzmann
Prof Dr Hans Rudolf Widmer
Prof Dr Leo Bühler
Ms Pascale Tilmant

Prof Eliane J. Müller

President Scientific Committee
Head SCRM Platform

PD Dr Marisa Jaconi

Member Scientific Committee
Vice-Director SICT

Scientific Committee

Prof Eliane J. Müller
Prof Dr Gabriela Baerlocher
Prof Dr Eduardo Moreno
PD Dr Marisa Jaconi
Dr Stefano Di Santo
Dr Jean-François Brunet

PROGRAM

Bridging Cell-based Therapies in Switzerland and beyond: Current and future perspectives

Session 1

Chairperson: Prof Eliane J. Müller and PD Dr Marisa Jaconi

Schedule	Speakers	Title/Location
09:00–09:15	Coffee	REGISTRATION
09:15–09:20	Prof Thomas Krause	Joint Meeting Welcome
09:20–09:25	Ms Thérèse Meyer-Kaelin	SICT Welcome
09:25–09:35	Prof Andreas Tobler Medical Director Inselspital	Insel Gruppe Welcome
09:35–10:15	Hot Topic: Prof Hinrich Abken University of Cologne Clinical Partner: Prof G. Baerlocher	The fourth generation of CAR T cells: TRUCKs can activate the innate response towards tumors
10:15–10:45	Coffee Break	
Cell-based Projects in Swiss Therapy Centers: State of the Art		
10:45–11:00	Prof Simon Hoerstrup	Wyss Center Zurich
11:00–11:15	Prof Giuseppe Vassalli	Cardio Centro Lugano
11:15–11:30	Dr Jean-François Brunet	CPC Lausanne
11:30–11:45	Prof Gabriela Baerlocher	University Hospital Bern
11:45–12:00	PD Dr Nina Khanna Dr Sylvie Miot	University Hospital and University of Basel
12:00–13:00	Representatives: Inselspital, University Hospital Bern, Sitem-Insel, Swiss Cell Therapy Centers, Pharmaceutical Industries Moderation: Prof E. J. Müller	Round table discussion: Establish a cooperative network between Swiss Cell Therapy Centers
13:00–14:00	Lunch Break	

Session 2

Chairperson: Prof Eduardo Moreno and Prof Gabriela Baerlocher

Schedule	Speakers	Title/Location
Successful Cell Therapies		
14:00–14:35	Prof Dr Lorenz Studer Memorial Sloan-Kettering CC, NY Clinical Partner: Prof C. Bassetti	Developing a cell based therapy for the treatment of Parkinson's disease
14:35–15:10	Prof Outi Hovatta Karolinska Institute, Stockholm Clinical Partner: Prof S. Wolf/ Prof V. Enzmann	Xeno-free retinal pigment epithelial cells differenti- ated from human embry- onic stem cells (hESC), for treatment of age-related macular degeneration
15:10–15:45	Dr Jan Tchorz Novartis, Basel Clinical Partner: Prof D. Candinas/ PD D. Stroka	Spatiotemporal regulati- on of hepatic Wnt/ β - Catenin signaling during homeostasis and regeneration
15:45–16:15	Coffee Break	
16:15–16:30	Dr Sufian S. Ahmad Inselspital, University Hospital Bern	From laboratory bench to clinical practice: Healing of the ACL-A Paradigm Shift
16:30–16:45	Dr Nicolas Mach Geneva University Hospital	Cancer immunotherapy
16:45–17:20	Prof John McGrath King's College, London Clinical Partner: Prof L. Borradori	Clinical trials for inherited blistering skin diseases: making therapeutic progress
17:20–17:30	Prof Thomas Krause	Closing remarks

ABSTRACTS

The fourth generation of CAR T cells: TRUCKs can activate the innate response towards tumors

Prof Dr Hinrich Abken, Center for Molecular Medicine Cologne (CMMC), University of Cologne, and Clinic I for Internal Medicine, University Hospital Cologne, Cologne, Germany

Adoptive therapy with CAR engineered T cells can substantially reduce the tumor burden as long as the targeted antigen is present on the cancer cells. However, cancer cells which lack the cognate antigen are invisible to CAR T cells; those cancer cells may contribute to deadly tumor relapses.

We discuss the fourth generation of CAR T cells, so called TRUCKs, which release inducible IL-12 upon CAR engagement in the targeted tumor lesion. Locally accumulating IL-12 in turn attracts an innate immune cell response towards those cancer cells that are invisible to CAR T cells. Elimination of antigen-loss tumor cells was accompanied by the accumulation of activat-

ed macrophages through a TNF-alpha mediated process. The locally restricted deposit of IL-12 by CAR T cells has the advantage to target otherwise not accessible tumor lesions, to achieve therapeutic levels in the targeted lesion, to reduce systemic toxicity and to recruit and activate innate immune cells. The strategy combines antigen-redirectioned immunotherapy with an antigen-independent anti-tumor response. Other cytokines may also be delivered.

We discuss the potential benefit in combining cytokines, the major consequences for future strategies, the immune therapy of malignant diseases and other applications of TRUCKs as targeted living factories.

The Wyss Zurich Model

Prof Dr Simon P. Hoerstrup, Institute for Regenerative Medicine, University of Zurich, Zurich, Switzerland

The Regenerative Medicine Technologies Platform of Wyss Zurich is a fully certified state-of-the-art technical and scientific platform dedicated to manufacturing clinical grade products that meet the required stringent regulatory standards. The Platform provides the expertise and guidance required to respond to the unique and diverse challenges presented by the clinical translation of projects in the field of regenerative medicine.

As a lean, academic translational research facility for Good Manufacturing Practice (GMP), the Regenerative Medicine Technologies Platform aims at the efficient translation of basic biomedical research to applied regenerative therapies. The enrolment of clinical studies in the field of regenerative medicine and technologies according to Good Clinical Practice (GCP) is undertaken in collaboration with Swissmedic and the related international authorities (e.g. EMA, FDA).

Clinical cell therapy trials at the Cardiocentro Ticino, Lugano

Prof Dr med Giuseppe Vassalli, Cardiocentro Ticino, Lugano and Lausanne University Hospital (CHUV), Lausanne, Switzerland

The Cardiocentro Ticino at Lugano has completed 3 clinical trials of autologous mononuclear bone marrow cells (BM-MNC) in heart disease patients. The development of the first Good Manufacturing Practice-grade cell factory certified by Swissmedic at the Cardiocentro was instrumental to the conduction of these trials.

The monocentric Stem Cell Transplantation in Ischemic Myocardium (STIM) trial was the first cell therapy trial in cardiological patients in Switzerland. Twenty-three patients with acute myocardial infarction (AMI) were treated with intracoronary infusion of BM-MNC within a median of 3 days. The procedure was safe (Swiss Med Wkly 2012;142:w13632).

The second trial was the Swiss multicenter Intracoronary Stem cells Study in Acute Myocardial Infarction (Swiss-AMI) trial. We randomized 200 AMI patients AMI in a 1:1:1 pattern into an open-labeled control and 2 BM-MNC treatment groups where cells were either administered

5–7 days or 3–4 weeks after AMI. Among patients with AMI and ventricular dysfunction, treatment with BM-MNC either 5–7 days or 3–4 weeks after AMI did not improve cardiac function at 12 months, compared with control (Circulation Research 2016;119:481-90).

The third trial was a safety/feasibility phase trial of percutaneous catheter-based intramyocardial BM-MNC injection in chronic heart failure patients (n=10). The procedure proved to be feasible and safe.

The Cardiocentro Ticino will participate in the multinational, multicenter, double-blind, placebo-controlled, randomized BAMI trial of intracoronary BM-MNC therapy in AMI patients.

Ongoing pre-clinical research includes the study of exosomes secreted by human cardiac progenitor cells, and c-kit+ human cardiac progenitor cells derived from endomyocardial biopsy samples.

Cell production center at CHUV, Lausanne

Dr Jean-François Brunet, Director of the Centre of Cellular Production, LAC/DL, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Since 1985, Lausanne University Hospital (CHUV) has a laboratory that is a reference in Switzerland for the treatment of severe burns. To further develop their skills in regenerative medicine, CHUV has included in its priority projects as part of its strategic plan 2009-2013, the creation of a «Cell Production Center (CPC)» to encounter the legal and GMP requirement whose objectives are both:

- Sustain the production activity of autologous epidermis for burns center at CHUV in ensuring their production based on GMP (Good Manufacturing Practice) requirements by Swissmedic.

- Produce the cells/tissues to GMP standards in other areas of application for clinical trials. The results obtained in preclinical and basic research by several teams of clinicians/researchers from the CHUV are very promising as in the field of orthopaedic and neuroscience applications.

Since 2012, the CPC at CHUV obtained the GMP certification for production of standardized transplant from Swissmedic and now, the challenge is to obtain each authorization for the clinical trials.

Cell-based therapies for cartilage repair or infections – ongoing clinical trials at University Hospital Basel

*PD Dr med Nina Khanna, University Hospital Basel
Dr Sylvie Miot, Department of Surgery and Biomedicine,
University Hospital Basel, Basel, Switzerland*

Clinical studies using chondrocytes-based therapies are aiming to assess whether engineered autologous nasal chondrocytes-based cartilage grafts allow safe and functional cartilage repair. Autologous nasal cartilage grafts are engineered in a clean room at the Department of Biomedicine. In a first phase I clinical study, autologous nasal cartilage grafts were used as an alternative to native cartilage for the reconstruction of the alar lobule of the nose after skin tumor resection, leading to complete structural, functional and aesthetic recovery. Similar cartilage grafts were implanted in 18 patients for the repair of articular cartilage defects after traumatic injuries in the context of a safety and feasibility phase I study. Promising results have led to EU funding of a multicentre phase II study.

Opportunistic infections remain a leading cause of morbidity and mortality in transplant recipients. Clinical studies using adoptive transfer of pathogen-specific T cells aim at restoring immunity and thereby preventing and treating infections. In the current Phase I/II study, we investigate the safety and feasibility of direct infusions of donor-derived pathogen-specific IFN- γ positive selected T-cells under GMP requirements using the clinically certified Miltenyi® cytokine capture system in recipients of hematopoietic stem cell transplantation with post-transplant adenovirus, cytomegalovirus (CMV) or Epstein Barr virus infections. So far, three patients have been treated for treatment refractory CMV infection.

Established and Certified Procedures for Collection, Processing and Transplantation of Autologous Hematopoietic Stem Cells as Platform for Novel Personalized Cellular Immunotherapies

Prof Dr med Gabriela M. Baerlocher, Deputy Head of Hematology and Director of the Clinical Stem Cell Laboratory, Department of Hematology and Clinical Research, Inselspital, University Hospital, University of Bern, Bern, Switzerland

High-dose chemotherapy and autologous hematopoietic stem cell transplantation is a well-established treatment strategy for malignancies such as multiple myeloma, lymphoma and leukemia. The success of this approach depends to a great extent on the ability to mobilize sufficient CD34+ stem and progenitor cells from the bone marrow to the peripheral blood, on the optimal collection technique to gain enough CD34+ mononuclear cells within a few hours, on sophisticated laboratory techniques to process and freeze sterile transplants with adequate numbers of CD34+ cells and to thaw and transplant enough viable hematopoietic stem and progenitor cells which home to the bone marrow and rescue the chemotherapy eliminated hematopoiesis.

The first autologous transplantation at the Inselspital was performed in 1982 and in 2015 145 transplantations have been performed in our center which is the largest autologous transplantation center in Switzerland. In addition, the autologous stem cell transplantation program of the Inselspital was the first JACIE accredited center in Europe in 2004 and so far more than a thousand cellular products have been successfully collected, processed and transplanted. Over the years continuous and persistent technical, qualitative and medical refinements and improvements such as the use of automated washing stations, devices for DNA-based viability assessments, computer-based planning and documentation of all procedures as well as personalized preparations of cellular transplant products paved the way for the successful growth of this program and cellular platform.

Developing a cell based therapy for the treatment of Parkinson's disease

Prof Dr med Lorenz Studer, Director Center for Stem Cell Biology, Memorial Sloan-Kettering Cancer Center, New York, USA

Human pluripotent stem cells (hPSCs) provide unprecedented access to the variety of cell types that comprise the human body. Over the last few years we have established a suite of protocols to reliably derive several dozens of cell types on demand and at scale, including neural, neural crest and sensory placode-derived lineages. Those studies illustrate how developmental pathways can be co-opted to drive the fate of hPSC-derived lineages in vitro in a manner that closely matches the developmental steps required to establish the equivalent tissues in vivo.

Here, I will discuss recent progress in the lab on the application of human PSC derived lineages for regenerative medicine. Those studies include the recent success in generating human enteric nervous system lineages for use in preclinical models of Hirschsprung's disease. Furthermore, I will provide an update on our efforts to develop a clinical cell therapy for the treatment of Parkinson's disease. The work in PD has moved from in vitro and early proof-of-concept in vivo studies into clinical grade cell manufacturing and the testing of the final cell product in FDA-required, IND-enabling studies which represent the final step prior to initiating a first in human clinical trial in PD patients.

Xeno-free retinal pigment epithelial cells differentiated from human embryonic stem cells (hESC), for treatment of age-related macular degeneration

Prof Dr med Outi Hovatta, Department of Clinical Science, Intervention and Technology, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden

For human treatment, xeno-free cell products are the safest. Standardised equal culture quality is important not only for cell transplantation but also to achieve stable and comparative research results. Good manufacturing practice (GMP) is a quality system that enables production of transplantable cells.

We have derived and differentiated human retinal pigment epithelial (RPE) cells in GMP conditions in the Vecura accredited GMP laboratory at Karolinska University Hospital at Huddinge. For derivation of the hESC lines, we have used human recombinant laminin LN521 (Biolamina) as a substrate, and iPSBrew (Miltenyi) culture medium. The cell lines have been characterised and differentiated to RPE by reducing

the growth factors from the medium and letting them spontaneously differentiate to embryoid bodies on the LN surface. The pigmented areas have been mechanically cut out to next culture at passage 3–5 for formation of a premaster cell bank. Safety and sterility test were performed at this stage for the Master and working banks, and the first cryopreservations have been performed. At passage 6–8, the cells were expanded on 1x15cm plates, and the master bank was frozen. Full characterization was performed.

Transplantation tests to the eyes of rabbits, rats, mice and chicken embryos have been performed. The first clinical trial in Stockholm has been planned.

Spatiotemporal regulation of hepatic Wnt/ β -Catenin signaling during homeostasis and regeneration

Dr Jan Tchorz, Developmental and Molecular Pathways, Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, Switzerland

The liver has a remarkable plasticity with an intrinsically high capacity for context-dependent regeneration. Impaired liver regeneration in patients and shortage of life-saving liver transplants requires therapeutic concepts for improving this process. Lgr5+ liver progenitor cells can be expanded ex vivo for subsequent transplantation. Furthermore, improving the regenerative capacity of diseased livers is an attractive strategy to overcome problems associated with cell transplantation. However, the potential of different liver cells to drive this process is highly debated and the underlying mechanisms poorly understood. Wnt/ β -Catenin signaling promotes proliferation and tissue homeostasis in the liver, but the

underlying mechanisms regulating hepatic Wnt pathway activity remain unclear. Using isolated liver progenitor cells and integrated in vivo approaches comprising lineage tracing, tissue-specific loss-of-function and pathway activation, we have now identified the instructive mechanism controlling the spatiotemporal regulation of hepatic Wnt/ β -Catenin signaling. Pathway activation increased liver size and improved liver regeneration, whereas inhibition caused the opposite effects, resulting in hypoplastic livers. Moreover, our data shows that hepatocytes throughout the liver equally contribute to liver homeostasis and have similar regenerative capacity.

From laboratory bench to clinical practice: Healing of the ACL – A Paradigm Shift

*Dr med Sufian S. Ahmad, Department of Orthopaedic Surgery,
Bern University Hospital, Inselspital, Bern, Switzerland*

One of the most common sport injuries with devastating impact on sport careers is injury of the anterior cruciate ligament (ACL). The rapid progression of osteoarthritis after ACL injury, alongside the debilitating immediate functional consequences of knee instability moved the area of ACL research into a spotlight position in the field of sports traumatology. It soon became clear that the combination of both the natural biological environment of the knee joint, as well as the biomechanical function prohibit the formation of a fibrin clot and therefore inhibit the formation of a biological scaffold.

Cyclic loading of the ACL during natural knee movement, also result in failure of premature fibrin or scar tissue. We worked on solving both issues by providing a biomechanical solution using a shock-absorbing

device to shield cyclic forces off the ACL during ligament healing. Proposed biological solutions to the problem include augmentation of the ACL with the use of a biological scaffold, which acts as a 3-dimensional architectural matrix for stem cells and ligamentocytes, alongside the application of platelet rich fibrin (PRF) and platelet rich plasma (PRP). Our primary In-vitro results show that the application of PRP to ligamentocytes cultivated in collagen scaffolds, is associated with the induction of cellular metabolic activity with increase in DNA content. The use of collagen scaffolds in our first clinical studies has shown improved clinical outcome in patients with ACL rupture. The addition of PRP and PRF will be evaluated in following clinical studies. The results of our work reflect on promising future regenerative approaches in the field of musculoskeletal medicine.

Cell-encapsulation technology for personalized cancer immunotherapy: Clinical data from Phase I study

*Dr med Nicolas Mach, Department of Internal Medicine Specialties,
Geneva University Hospital, Geneva, Switzerland*

Combining subcutaneous injection of irradiated autologous tumor cells and a biocompatible, clinical grade capsule containing allogeneic cells genetically modified to produce the strong adjuvant GM-CSF allows personalized therapy of any cancer types without custom made gene engineering. This innovative approach, developed in close collaboration between HUG, EPFL and MaxiVAX, delivers stable, standardized levels of GM-CSF at the vaccination site in combination with tumor specific antigens. Capsules are retrieved after one week. Sub-cutaneous Immunization with both irradiated tumor cells and capsules is repeated 6 times at weeks 1, 2, 3, 4, 6, 8. The first in human

Phase I study was performed in Geneva with manufacturing of the investigational medicinal product at the Cell Therapy Centre of HUG. Primary endpoints regarding safety and tolerability were met in this heavily pretreated population. Subcutaneous implantation and explantation of cell containing capsules was performed without technical difficulty. Very encouraging clinical results were also observed in this population of cancer patients with tumor progressing despite all standard therapies. The first Phase II efficacy study is planned in Switzerland in close collaboration with the Swiss Group for Clinical Cancer Research(SAKK).

We warmly thank our sponsors for support

